REMARKS

Applicant respectfully requests reconsideration. Claims 90, 93, 96, 98-101, 104, 133-146 and 149-151 were previously pending in this application. Claim 143 has been canceled. As a result, claims 90, 93, 96, 98-101, 104, 133-142, 144-146 and 149-151 are still pending for examination with claim 104 being an independent claim. Applicants have amended the specification to add subject matter incorporated by reference from parent application US6194388. No new matter has been added.

Claim Objections

Claim 143 has been objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 143 has been canceled. Accordingly, the objection is now moot.

Rejection Under 35 U.S.C. 112

Claims 133, 135, 137 and 139 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner has objected to Applicant's reference to the subject matter that was incorporated by reference without amendment of the specification.

The specification on page 1, 1st paragraph includes an incorporation by reference of U.S. Patent Application serial number . 08/386,063, filed February 7, 1995 which is now issued as US 6194388. According to the Examiner in accordance with 37 CFR 1.57(a) the subject matter recited in the claim and incorporated by reference should be added to the specification. Accordingly Applicant has added support for the limitation "wherein the CpG oligonucleotide does not include a GCG trinucleotide at a 5' and/or 3'terminal of the oligonucleotide" to the specification. The language added to the specification is found in the summary of the invention of US 6194388.

Accordingly, withdrawal of the written description rejection under 35 U.S.C. §112 is respectfully requested.

Claims 90, 93, 96, 98-101, 104 133-146 and 149-151 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, Applicant has not provided a disclosure that would enable the skilled artisan to practice the claimed invention without an undue burden of experimentation.

The Examiner has maintained the rejection of the claims of record under 35 U.S.C. §112. Pages 15-26 of the Office Action dated January 4, 2007 repeat the entire enablement rejection found in the Office Action dated March 27, 2006. The Examiner has not addressed significant portions of the arguments presented by the Applicant. Since the rejection is maintained Applicant has reiterated prior arguments below. Additionally, Applicant points out that each point of the prior rejection was addressed and rebutted by Applicant. The Examiner must address Applicant's arguments or withdraw the rejections. "If a *prima facie* case is made in the first instance and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed." *In re Hedges*, 783,F. 2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986).

Pages 4-14 of the Office Action address the Examiner's reasons for maintaining the rejection for lack of enablement. Each of these issues is addressed herein. The reasons for maintaining the rejection are addressed first.

Response to the Examiner's reasons for maintaining the rejection:

a. undue experimentation

The main reason for maintaining the rejection provided by the Examiner is that practice of the claimed invention requires undue experimentation because the specification "has not taught or shown the skilled artisan how to do harness the immune stimulation activity or render a therapeutic efficacy for use in the treatment of bacterial infection." (Office Action page 6).

Although maintaining the rejection the Examiner has never actually stated what the undue experimentation was that is required to practice the claimed invention. The invention is directed to a method of treating bacterial infection by administering CpG oligonucleotides to the subject. Applicants taught in the specification that the oligonucleotides should be administered to a subject to treat bacterial infection. The invention was based on the discovery by applicant that CpG oligonucleotides stimulated a potent immune response and that Applicant asserted was predictive of

treatment of bacterial infection. Since the invention many others have reiterated Applicant's findings. The Examiner continues to assert that undue experimentation is required but never states what that experimentation is. It appears that in the absence of the an in vivo example in the specification of a treatment demonstrating cure of a bacterial infection the Examiner has decided the invention does not work. This is not the appropriate legal standard. The examiner is requested to explain what experimentation is required and why it is undue.

Applicant asserts that a correlation between CpG nucleic acids and their use in the treatment of bacterial infection is disclosed and enabled. The MPEP section 2164.02 teaches that: "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)".

Further, the Examiner has stated that "the mere contemplation of treatment is not sufficient to demonstrate that the specification is enabling for the claimed invention." (Office Action page 6). The specification is not a "mere contemplation of treatment" The specification includes data that is sufficient to support applicant's conclusion that the claimed compounds would be useful for treating bacterial infection. The Examiner has not provided any support for rejecting this assertion by Applicant. What is the scientific basis that the Examiner is relying on to conclude Applicant's data is a mere contemplation of an idea.

A therapeutic method need not be ready for clinical application in order to be enabled. See *In re Brana*, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the

expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."

b. teachings related to Th1/Th2

Applicant addressed in detail the assertion that the claimed invention was unpredictable based on the papers cited in the office action teaching that the administration of cytokines was unpredictable. The examiner has not addressed any of these arguments specifically. Rather, she has stated that Applicant's arguments were not persuasive because the instant case "does relies on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease." The fact that a Th1 cytokine may be involved in the immune response has nothing to do with administration of exogenous cytokines. It is requested that the examiner address each of the points made by applicant or withdraw that portion of the rejection.

Additionally Applicant notes that the Examiner has stated "At the time the invention was made, it is well known in the art that the CpG motif present in the oligonucleotide stimulates Th1 immune response, which induces the production of Th1 associated cytokines." Applicant points out for the record that this statement is incorrect. At the time of the invention those skilled in the art were not aware of the effects of CpG oligonucleotides. This is Applicant's invention.

c. references submitted by applicant

In the previous response, Applicant provided references that demonstrate that the claimed invention can be predictably practiced by the skilled artisan by relying on the routine art. However, according to the Examiner, the submitted references demonstrate that undue experimentation would be necessary to enable the claimed invention. Applicant address each of the Examiner's concerns.

The Examiner has interpreted Auricchio et al. as establishing that further characterization of the mechanism by which CpG indirectly promotes the killing of *M. Tuberculosis* is needed. However, the mere phrase "by which CpG indirectly promotes killing of *M. Tuberculosis*", as quoted by the Examiner, clearly shows that CpGs can be used to kill *M. Tuberculosis* and therefore can be used to treat a bacterial infection. In effect, the paragraph referenced by the Examiner (Page 918) states: "Our results demonstrate that CpG ODN induce human macrophages to kill intracellular

MTB". The "further characterization of the mechanism" refers to the scientific question, if, in addition to cited mechanisms like TLR-2, other mediators may play a role in the killing of MTB. This question of further characterization does not render the teachings of Auricchio et al. unpredictable.

The Examiner quotes from Klinman, Conover and Coban: "There are only a limited number of settings in which such short term protection may be of therapeutic benefit." This quote is not evidence that the claimed invention does not work. In fact it implies that there is a "therapeutic benefit, the "short term protection" of these benefits refers back to earlier experiments (pre 1999) and in this (1999) publication, Klinman et al. show that "By repeatedly administering CpG ODN two to four times/month we found that this protection could be maintained indefinitely." Therapeutic regimes for the treatment of bacterial infection had therefore been established (Klinman et al. published in 1999).

The Examiner also quotes from Raghavan et al. (p7021) "CpG oligonucleotides have no direct antibacterial effect". This quote misrepresents the findings of Raghavan et al. Indeed, the paragraph from which the quote is taken states: "We found that intragastic administration of CpG ODN without bacterial antigen codelivery results in a consistent reduction in the bacterial load in the stomachs of mice with established *H. pylori* infection. The ODN lacking CpG motifs had absolutely no protective efficacy, supporting the conclusion that the effects observed were mediated solely by the contextual CpG motif. Moreover, our in vitro studies indicated that CpG ODN has no direct antibacterial effect." This paragraph provides a teaching that CpG oligonucleotides provide a consistent reduction in bacterial load, and is supportive of the predictability of the art. The observation that CpGs have no direct antibacterial effect *in vitro* is not relevant. Applicant is not claiming a direct bactericidal effect. Rather, Applicant has taught that CpG influences the immune response in a manner that is useful for treating infection. In addition, the Examiner states that Raghavan et al. shows that reduction in the bacterial load occurred concomitant with both upregulation of RANTES production and rapid recruitment of immune cells, and that "no similar teachings can be found in Applicant's disclosure". However, Applicants disclosure page 52 reads: "In response to unmethylated CpG an increased number of spleen cells secrete .... RANTES." and "CpG DNA acts as an effective danger signal and causes the immune system to respond vigorously

to new antigens in the area". The current application therefore teaches both the upregulation of RANTES and recruitment of immune cells, as observed by Raghavan et al. Regardless, Applicant asserts in the specification that CpG is useful for treating bacterial infection. Since the time of the invention, others have made consistent findings.

When referring to Juffermans et al. the Examiner states that the protective immunity varies among IFN-gamma gene proficient and IFN-gamma deficient mice, and continues by noting that the claimed invention does not require a person to be proficient or deficient in a particular gene. It is not immediately clear to the Applicant how this argument reads on the predictability of the art and/or the enablement of the current claimed invention. Mice deficient in IFN-gamma genes are severely immunocompromised and are used as a research tool only, for instance to elucidate certain mechanisms. While the current application does not specifically mention that a person needs to be IFN gamma gene proficient, the absence of this statement does not preclude the enablement of the current claimed invention. A person of ordinary skill in the art would understand that most (if not all) subjects are IFN gamma gene proficient and would appreciate that in the rare case where a subject is not IFN gamma gene proficient a different treatment regime might apply. The Examiner also states that the application does not provide "any guidance or direction to establish the gene that the treatment must possess in order to benefit from the administration of a CpG". Applicant assumes that the Examiner is referring to genes that *subject* undergoing treatment must possess.

The Examiner continues the analysis of Juffermans et al. by stating that the claimed invention is directed at treating bacterial infection in a subject while Juffermans et al. is only teaching prevention of infection. However, Juffermans et al. is teaching the treatment of infection. As stated in the abstract: "CpG ODNs given 2 weeks after infection were still able to reduce mycobacterial outgrowth." which clearly pertains to treatment of a bacterial infection. The Examiner also notes that Juffermans et al. discloses different treatment regimes for different bacteria. Differences in treatment regimens for different bacteria are part of the routine art. A person of ordinary skill in the art will appreciate that a rapidly replicating microorganism like *Lysteri monocytogenes* may require a different treatment regimen than the more indolent *Leishmania major*.

Krieg et al. echoes the findings of Juffermans et al., according to the Examiner, and also notes that different types of populations (as exemplified by IFN gamma deficient mice) may require different treatment regimens. Applicant's comments on this argument are noted above. The Examiner continues by stating that Krieg et al. found that excessive immune activation by CpG oligonucleotides may be deleterious and notes that the claims in the current application do not specify any amount other than "sufficient to treat bacterial infection". However, a person of ordinary skill can rely on the routine art to find treatment regimens that are effective, thereby avoiding excessive immune activation.

According to the Examiner, Hayashi et al. recognizes the use of CpG oligonucleotides as an adjuvant to the treatment of *M. avium* infection with the conventional antimicrobial agent clarihtromycin. Applicant acknowledges this observation, but also points out that Hayashi et al. also shows that "Treatment with a single dose of ISS-ODN (CpG) significantly decreased intracellular growth of *M. avium* in BMDMs by 68%, compared to the number of CFU in infected cells treated with M-ODN (control) or medium alone", thus describing a treatment regimen for bacterial infection using CpG, offering further evidence of the predictability of the art.

The Examiner continues the analysis of the references by quoting from Klinman, Verthelyi, Takeshita and Ishii on the risk of using CpG or DNA vaccines to stimulate innate or adaptive immunity. The Examiner quotes from page 126 where the authors enumerate potential problems with vaccination in general. However, the quoted paragraph concludes with " Balancing these safety concerns, toxicity has not been observed in normal animals injected with therapeutic doses of DNA vaccine or CpG ODN. In addition, none of the human volunteers exposed to DNA vaccines or anti-sense ODN have suffered serious adverse consequences." Thus, this paragraph shows that the routine art recognizes that the safety concerns in treatment with CpG oligonucleotides are not a major issue. Furthermore, the MPEP (§2164.01) states: "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement. This is a regulatory issue that falls within a territory of the Food and Drug Administration.

Gursel et al. state that "The(se) immunostimulatory activities are being harnessed therapeutically", which the Examiner interprets as "The art is still trying to harness the immunostimulatory activities of CpG oligonucleotides to render therapeutic value". The teachings of Gursel et al. pertain to modifications of specific delivery methods resulting in an increase in bioavailability, but does not reflect any unpredictability in the art. In effect, the teachings of Gursel et al. also reiterate the teachings on treatment of bacterial infections using CpG oligonucleotides in the routine art.

Klinman and Kamstrup provide an overview of the state of the art in treating bacterial infections, by administration of CpGs. Their publication refers to the uses of CpGs as adjuvant, vaccine and therapeutic in infection subjects. For instance, on page 177, the authors refer to Zimmermann et al. (Zimmermann et al. 1998. J. Immunol.) who showed that a CpG protected susceptible mice from *leishmania* infection when administered several weeks after infection, which clearly shows that treatment of a bacterial infection with CpG was established in the routine art at the time of filing of the current application.

The final publication referred to by the Examiner is Elkins et al. Elkins et al. state that "the bacterial determinants that stimulate either inflammatory or lymphocyte dependent innate response are poorly understood." However, this quote is taken from the introduction of the publication, i.e. where the authors set out the scientific problem to be investigated. In the next paragraph, which summarizes their findings, the authors state that: "Here, we show that treatment of mice with either bacterial chromosomal DNA or oligonucleotide DNA containing unmethylated CpG motifs that stimulate Th-1 associated cytokine production, induces lymphocyte-dependent protection against lethal challenge with virulent *F. tularens* and *L. monocytogenes.*" The authors therefore provide an understanding of the bacterial determinants that stimulate either inflammatory or lymphocyte-dependent immune response. Since the authors publication predates the current application, the understandings were part of the routine art at the time of filing. The Examiner also notes that Elkins et al. mention that "preliminary data also suggests that oligonucleotide DNA containing does not protect against infection with two extracellular bacterial pathogens, enterohemorrhagic *E. coli* and *Yersinia enterocolitica* (data not shown)". To contrast this preliminary finding, Applications note that Raghavan et al. showed that infection by H. Pylori (an extracellular bacteria) could be treated

with CpG oligonucleotides. In addition, Applicants want to point the Examiner to Gomis et al. (submitted with the response of 9/27/2006), who show that bacterial infection by E, coli can be treated with CpG (See e.g. abstract).

Finally, the Examiner has concluded that "the deficiency of the specification cannot further be contemplated by the teachings of the art.

Applicants have not presented the data in the papers discussed above for purposes of enabling the claimed invention. The data is presented to rebut the rejection of record. The specification as filed provides adequate enablement for the claimed invention. The Examiner had asserted that the invention was unpredictable at the time of filing, as evidenced by teachings found in post-filing references. Applicants have asserted that one of skill in the art would have expected the invention to work as Applicants taught in the specification at the time the patent application was filed.

The Examiner has asserted that the claimed invention was "unpredictable" and supported this view with post-filing references to show that the invention would not be expected to work even after the filing of the patent application. The post-filing publications presented by Applicant demonstrate that the claimed methods actually do work as Applicant stated they would in the patent application. The teachings are consistent with the teachings and data described in the specification.

Rejections repeated from prior office action but not addressed:

As discussed above, the Examiner re-iterated the entire rejection under 35 USC 112 presented in the prior Office Action dated March 27, 2006. Other than the specific points discussed above, the Examiner has not addressed any of Applicants' arguments filed in response to the Office Action dated March 27, 2006. Thus, Applicants present arguments to address each of these rejections again. It is specifically requested that the Examiner address each of Applicants' arguments or withdraw the rejections.

State of the Art

The Examiner has made several statements about the state of the art. In order to address each statement, Applicants have copied the Examiner's statement and provide comments immediately below.

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, host response to exogenously administered cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state.
    - The statement is not relevant to the claimed invention. Applicants are not exogenously administering cytokines. The claimed invention relates to the delivery of an oligonucleotide which stimulates in vivo the promotion or inhibition of cytokine production.
- Both Th1 and Th2 type of immune responses is necessary. Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, a tight control over where and when Th1 and Th2 immune responses happen is necessary.
    - This teaching is not inconsistent with the claimed invention. The patent application teaches that CpG oligonucleotides promote an immune response when administered in vivo. The immune response involves a shift in the balance of Th1 and Th2 cytokines such that the Th1 response is favored. The shift is a natural one that occurs in response to a stimulus that Applicants believe a naturally existing stimulant, bacterial DNA. It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 35-36 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. The resultant immune response is a natural one. Not one that is dramatically skewed to cause tissue damage.

- The efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial. For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection.
    - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine, such as IL-, IFN, or IL-18. Additionally, the Aoki et al reference cited by the examiner actually teaches that cytokines have promise in the treatment of infectious disease. On page 231 2nd column it is concluded that "Undoubtedly, in the next several years we may witness the formal introduction of cytokines or their inhibitors to routine clinical use for infectious diseases other than viral hepatitis." and "Cytokines hold great promise to be used as therapeutics or immune adjuvant for vaccination against infectious disease.....Several cytokines have been successfully used for human conditions and it is anticipated that more will enter into clinical applications."
- Interleukin-12, Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation. Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice.
    - Again, the statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine such as IL-12.
- Interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18.
    - The statement is not relevant to the claimed invention. Applicants are not directly administering IL18. Administering a compound is very different than stimulating the body to produce the compound endogenously.

- Interleukin 6 and interferon gamma, both are Th1 associated cytokines, augment the susceptibility of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utilitising HIV-1 strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1.
  - The statement is not relevant to the claimed invention. HIV is a virus. Applicants claims are limited to the treatment of bacterial infection.
- Interleukin 2, a Th1 associated cytokine, increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. (Office Action citing Masihi)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. This point is clarified in the Masihi reference itself. In his review article Masihi describes several classes of molecules and how they are used for fighting infection. One section (section 3) is on the exogenous administration of cytokines as therapeutic agents. This is the section cited by the Examiner which describes some of the troubles associated with exogenous administration of cytokines. The next section (section 4) describes synthetic and natural immunomodulators. Section 4.1 is dedicated to CpG oligonucleotides. Unlike all of the problems highlighted by Masihi related to cytokines, Masihi describes studies in which CpG ODN were demonstrated to protect against *Listeria moncytogenes* and *Francisella tularensis* in mice. Additionally studies are described relating to successful protection against *Trypansoma Cruzi* and *Leishmania major*. The author even concludes "CpG-ODN were even curative when given after lethal *Leishmania major* infection.: (page 647 1st full sentence).
- Interferon gamma is ineffective against the virulent strain of Mycobacterium avium. Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma.

- The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. Additionally the cited statement from the Silva reference is incorrect. On page 5583 last sentence left column Silva et al actually states that "virulent strains resist the antimycobacterial activity of *IFN-γ-activated macrophages*" (emphasis added.) IFN-γ-activated macrophages are different than IFN-γ.

Based on the above assertions, the Examiner concludes that "the art amply recognizes the following limitations: inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects." None of the above-statements support the above conclusions. In each instance but one (the one referring to Infante-Duarte et al.) the Examiner is describing a system of one or more exogenously administered cytokines. Applicants have not claimed the administration of cytokines. Applicants claims are directed to the administration of oligonucleotides which produce a shift in the balance of cytokine production and cellular activation in a natural environment. The body controls how much of a particular cytokine to produce. The effect is different from administering cytokines. The ability to stimulate an immune response without directly administering immune factors such as cytokines is an advantage of the invention. The teachings of Infante-Duarte et al. cited by the Examiner are not inconsistent with the claimed invention and also don't support the above-conclusion.

Additionally, the Examiner has cited several teachings in the CpG art. Applicants addresses each of these below.

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines. However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice. Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next. (Office Action, citing Mutwiri et al)

- Mutwiri et al actually state "TLR9 has yet to be identified in species other than human and mice, *but it is assumed that a similar signaling mechanism is involved in other species*". (Emphasis added) The Examiner's conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced. The reference does not teach that TLR9 is absent is some species. Additionally the reference is a review article describing studies that have examined the effects of CpG therapies in a variety of animals, including mice, humans, cattle, sheep, pigs, horses, goats, rabbits, fish, dogs, cats, and chickens (see for instance page 90 first full paragraph of left column and first 20 lines of right column). The authors conclude in that paragraph in the right column of page 90 that "Together, these data suggest that in vitro stimulation of cells by CpG motifs is conserved across species, and that the enhanced activity of GACGTT in laboratory animals may be an artificial bias due to inbreeding."

- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. The art frequently notes that the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif, influence both the level and type of immune stimulation; the spacings between CpG motifs surrounding the CpG motif influence both the level and type of immune stimulation; and the type of cytokine stimulated by oligonucleotides containing the CpG motif varies from one oligonucleotide to the next. The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence.
  - Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response and be used to treat disease

is not only described (e.g., see page 8, lines 5-16 and page 40-42) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The fact that there is some variability in the responses depending on the sequence of the oligonucleotide is not surprising. If one were proceeding in a clinical trial one would have to select a single oligonucleotide to use. However, this is not the standard for enablement. Variability with drugs in humans is not unusual. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A human's immune status on any particular day can determine the human's response to a drug.

- In vitro observations do not accurately predict what happens in vivo. (Office Action, citing Mutwiri et al)
  - The cited statement is true for any biological agent. A regulatory authority such as the FDA would not approve a drug simply on the basis of in vitro tests. However, this is not the standard for patentability. The statement is not specific and has no bearing on the enablement of the claims.
- The immunostimulatory activity of CpG oligonucleotides is species specific. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice. (Office Action, citing Mutwiri et al)
  - The statement does not provide support for lack of enablement. Simply because one embodiment might be optimal or preferred does not make other embodiments non-enabled. Additionally, the statement taken from Mutwiri et al reflects the analysis of data from several published articles. It does not purport to analyze each and every CpG ODN.

- The immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another. (Office Action, citing Mutwiri et al)
  - As described above, variability is expected. However, it has been described in the specification and confirmed in numerous references that CpG containing oligonucleotides stimulate an immune response. The consistent effect is attributed to the presence of the unmethylated CpG motif in the oligonucleotide.
- Oligonucleotides containing the CpG motif increase the susceptibility to infection by *Candida albicans*. Ito et al. notes that although oligonucleotides containing the CpG motif promote Th1 immunity, the induction of IL-12 by the oligonucleotide increases infection by *Candida albicans* in mice, rather that protecting the mice from said infection. (Office Action, citing Ito et al)
  - *Candida albicans* is a yeast, not a bacteria. The claimed invention is directed to the treatment of bacterial infection using CpG oligonucleotides. Ito et al states that CpG ODN "treatment typically improves host resistance to infection by bacterial, viral, and parasitic pathogens." (page 6154, left column, first paragraph last sentence)

Thus, none of the references or passages cited by the Examiner support a conclusion of the lack of enablement of the claimed invention.

Presence or absence of working examples:

The Examiner has stated that the "specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection....All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif."

Applicants have taught that in addition to induction of IFN-gamma the working examples in the specification show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. The specification asserts that CpG oligonucleotides are useful in treating bacterial

infections. The combination of the changes in immune parameters demonstrated with CpG oligonucleotides is sufficient to support applicants assertion at the time of the invention that CpG oligonucleotides would be useful in the treatment of bacterial infection. Applicants assert that a correlation between CpG and their use in the treatment and/or prevention of bacterial infection is disclosed and enabled.

Amount of direction or guidance presented:

Applicants have provided sufficient direction and guidance in the specification. Applicant has described the structural properties of CpG oligonucleotides and have taught that they can be used to treat bacterial infection. Further applicants have provides preferred modes of administration and formulations. Those of skill in the art are well aware of such routine methods of formulating and administering drugs.

Predictability or unpredictability of the art:

The Examiner has stated that "As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable." Applicants disagree. Applicant has addressed each statement by the Examiner from the prior art which was put forth to support this conclusion of lack of predictability. There is no evidence of unpredictability of the invention. The variability observed with CpG oligonucleotides is not sufficient to demonstrate unpredictability. It simply shows that some oligonucleotides work better than others at stimulating the immune response. Applicants have identified the key structural property , the unmethylated CpG dinucleotide, that allows this class of oligonucleotides to function through TLR9 to stimulate an immune response that is useful in the treatment of bacterial infection.

Quantity of experimentation necessary:

The Examiner has provided several reasons for why additional experimentation would be necessary. For instance it is stated in the Office Action that "Applicant has not provided any guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections...pertaining to the type of

activity that would need to be stimulated to provide effective treatment against bacterial infections....relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections." It is unclear how any of these factors relate to extensive experimentation. Applicants have taught how to make the CpG ODNs using routine methods known in the art. Applicants have also taught that they produce a pattern of immune stimulation and that they can be administered for the treatment of bacterial infection. One of skill in the art would simply need to make the ODN or buy it and administer it to a subject having a bacterial infection. The skilled artisan would know the best routes of administration to use depending on the infectious agent and the subject.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a bacterial infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is capable of treating bacterial infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is effective in treating bacterial infection. Therefore, the amount of experimentation required to practice the invention is not undue.

Additionally, Applicants enclose herewith copies of several references demonstrating the positive effect of CpG oligonucleotides in the treatment of bacterial infection (listed on attached IDS and including Cellular Microbiology 2003 5(12) 913-920, Diseases of Aquatic Organisms 2003 56(1) 43-48, Immunity 1999 11 123-129, Infection and Immunity 1999 67(11) 5658-5663, Infection and Immunity 2000 68(5) 2948-2953, Infection and Immunity 2001 69(10) 6156-6164, Infection and Immunity 2002 70(1) 147-152, Infection and Immunity 2003 71(2) 857-863, Infection and Immunity 2003 71(12) 7014-7022, Journal of Immunology 1998 161(5) 2428-2434, Journal of Immunology 1999 162 2291-2298, Journal of Immunology 2000 165(8) 4537-4543, Journal of Immunology 2001 167(6) 3324-3328, Springer Semin Immunopathol 2000 22(1-2) 173-183.). The post-filing references are not cited in order to enable the claims but to rebut the rejection that the

post-filing references cited by the Examiner as being sufficient to demonstrate the unpredictability of the claimed invention.

Accordingly, withdrawal of the enablement rejection under 35 U.S.C. §112 is respectfully requested.

Double Patenting Rejection

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/613916. The rejection is a provisional one since none of the claims in the 10/613916 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 10/224523. The rejection is a provisional one since none of the claims in the 10/224523 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 10/787737. The rejection is a provisional one since none of the claims in the 10/787737 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/735592. The rejection is a provisional one since none of the claims in the 10/735592 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 has been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 41 of copending Application No. 10/894682.

Application No. 10/894682 is not filed by Applicant of the current application. Applicant assumes that the Examiner is referring to Application No. 10/894862. The rejection is a provisional one since none of the claims in the 10/894862 application have been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

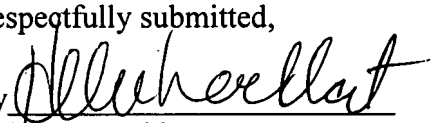
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: June 11, 2007

Respectfully submitted,

By 

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